The plasma free 5HT ranged from 38–148 ng/ml in the control rats compared with a range of 35–138 ng/ml in the test animals. There is no significant difference between the mean values of 59 and 62 ng/ml which were obtained with the control and test groups, respectively (Figure 2).

The platelet-bound 5HT levels ranged from 675–1393 ng/10^9 platelets in the control rats, with a mean value of 1007. The test rats showed a range of 606–1725 ng/10^9 platelets and a mean of 1183. There is no statistically significant difference between these 2 groups of figures (Figure 3).

Comment. All the test rats showed evidence of right ventricular hypertrophy which indicates that the diet of *C. spectabilis* seeds had induced pulmonary hypertension. This was not associated with an alteration in the concentration of 5HT in the plasma or platelets. The circulating free and bound 5HT levels are subjected to a number of counteracting equilibrating mechanisms viz. state of tissue 5HT liberation, rate of platelet uptake and release, and enzymatic degradation. The equilibrium maintained by the complex interplay of these factors makes it difficult to detect local changes in blood 5HT levels. The results of the present experiment therefore do not entirely exclude the possibility that 5HT may be concerned in some way with the development of the pulmonary hypertension.

It has recently been shown[14] that mast cells are not concerned in the genesis of the pulmonary hypertension produced in rats by ingestion of *C. spectabilis* seeds, but that their proliferation is a secondary phenomenon related to the exudative lesions which occur in the lungs coincident with the terminal onset of right ventricular failure.

In a further experiment the concentration of 5HT was measured in the lung tissue of 6 normal rats and 5 rats fed on *C. spectabilis* seeds for 34 days. The test rats showed evidence of pulmonary hypertension but the lung 5HT concentrations did not differ significantly from those observed in the controls.

Zusammenfassung. Der pulmonare Blutdruck in Ratten kann durch Abfütterung von *Crotalaria spectabilis* erhöht werden, ohne die Konzentration des plasmafreien und an die Thrombozyten gebundenen 5-Hydroxytryptamins zu verändern.

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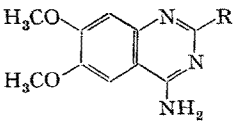
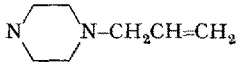
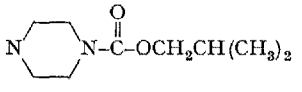
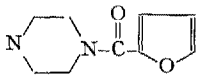
Pharmacological Studies with Some New Antihypertensive Aminoquinazolines

Following our investigation of the blood pressure-lowering properties of 2-amino-4(3H)-quinazolines[1], we extended our studies to a related family of 4-amino-quinazolines. This paper offers a preliminary account of the pharmacological activity of 4 members of the new series. Their chemical structures are presented in the Table.



Chemical name	R
I 2-dimethylamino-4-amino-6,7-dimethoxyquinazoline monohydrochloride.	$N(CH_3)_2$
II 2-(4-allyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline dihydrochloride.	
III 4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-piperazine-1-carboxylic acid, isobutyl ester, monohydrochloride.	
IV 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine monohydrochloride.	

Blood pressure in the coccygeal artery was measured in conscious hypertensive[2] dogs with an electrosphygmograph and a pneumatic pulse transducer[3], and was recorded before, and at 2, 6 and 24 h after administration of a drug orally by capsule, or by gastric gavage. Each of the compounds was evaluated at 4–6 different doses in at least 10 dogs.

The dye dilution method of HAMILTON[4] was used to study the effect of drugs on cardiac output of normotensive dogs anesthetized with sodium pentobarbital, 30–35 mg/kg, i.v. Continuously recorded indocyanin-green dye curves were obtained with a Waters oximeter cuvette installed into the right femoral artery. Total peripheral vascular resistance was calculated according to the procedure of GREEN[5]. Blood flow in a femoral artery was recorded with a Shipley-Wilson flowmeter; drugs were injected intra-arterially in volumes not exceeding 0.1 ml.

The effects of drugs administered i.v. on contractions of the nictitating membrane induced by electrical stimulation of the sympathetic chain were investigated in cats anesthetized with chloralose, 75 mg/kg i.v. The cervical sympathetic chain was stimulated above and below the

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superior cervical ganglion with supramaximal electrical stimuli, 25/sec, for 20 sec, with an automatic stimulator[6]. Spinal cords of cats, anesthetized with ether, were pithed by passing a steel wire into the spinal canal via the foramen magnum.

Sympathetic cardio-accelerator nerves in vagotomized dogs, anesthetized with chloralose, 75 mg/kg i.v., were stimulated postganglionically for 20 sec with square wave impulses, 1–8 V, 10/sec, 1 msec duration. Blood pressure and heart rate were recorded with a Grass polygraph.

At 0.3 mg/kg orally, all 4 compounds lowered systolic blood pressure in conscious hypertensive dogs. The maximum hypotensive effect was obtained 2–6 h after treatment, and ranged from 10–60 mmHg. III and IV were the most potent of the 4 compounds; the minimum effective dose of either was 20 μg/kg orally, and the maximum hypotensive effect was obtained with 0.15 mg per kg orally. All 4 compounds were more potent than hydralazine. The duration of the hypotensive effect was dose dependent, and varied from compound to compound. I and II had a shorter duration of action than III and IV. At 0.625 mg/kg, the hypotensive effect of both III and IV persisted for at least 24 h. By oral administration to conscious dogs all 4 compounds had no significant effect on the heart rate. In contrast, hydralazine, 1.25 mg/kg orally increased the heart rate by more than 50 beats/min and for longer than 6 h. By i.v. administration to anesthetized dogs all 4 compounds increased heart rate, but by only 10 beats/min and for less than 5 min. Hydralazine, 1 mg/kg i.v. increased the heart rate by approximately 15 beats/min and for longer than 30 min.

All 4 aminoquinazolines at doses of from 0.4–4.0 mg/kg i.v. lowered blood pressure and calculated total peripheral vascular resistance in dogs. Intravenous administration of II, 1 mg/kg, or of IV, 0.4 mg/kg, moderately increased cardiac output; but neither III, 0.4–1.6 mg/kg, nor I, 0.25–1.0 mg/kg, had a significant effect on cardiac output. Femoral arterial blood flow increased following intra-arterial administration of either of the 4 compounds at doses ranging from 1–256 μg. In cats, the compounds either reduced or reversed the pressor effect of epinephrine, 5–10 μg i.v. but did not alter the pressor effect of angiotensinamide. Equal reductions of contractions of the cat nictitating membrane induced by pre- or postganglionic stimulation suggested that the drugs had no conventional hexamethonium-like ganglionic blocking activity.

In pithed cats infused with epinephrine, all 4 compounds lowered blood pressure.

III, 0.1 mg/kg i.v. and II, 4.0 mg/kg i.v. reduced cardiac acceleration caused by stimulation of cardiac sympathetic fibers in dogs; IV at 0.1 mg/kg had no effect.

The mechanism of hypotensive activity of these compounds appears to involve a component of sympathetic inhibition at peripheral site or sites, but this action differs in important respects from conventional blockade of α-receptors. A detailed study of the site and mechanism of action of 1 member of this group will be published shortly[7].

Zusammenfassung. 4 neue Aminoquinazolin-Derivate, die den Blutdruck von Hunden und Katzen herabsetzen, werden beschrieben. Ihre wirksamen Dosen liegen im Bereiche von 20 bis 300 μg/kg peroral. Diese Substanzen setzen den peripheren Widerstand herab und reduzieren die blutdrucksteigernde Wirkung von Adrenalin, unterscheiden sich aber von den typischen α-Sympatholytika.

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Blockade of Uptake of Norepinephrine in Rodents by α,α-Dimethylphenethylaminopropan-2-one

In previous studies on the effects of 4-chlorinated aralkylamines on the monoamine levels in tissues of the rat it has been shown that 4-chloro-α,α-dimethylphenethylaminopropan-2-one (AY-14,948) blocks the uptake of norepinephrine into the heart[1]. Other 4-chlorinated aralkylamines have been shown to have effects on the monoamines in tissues and to differ in their actions[2–5]. In studies on the effects of compounds structurally related to AY-14,948 on the uptake and storage of the monoamines in rodent tissues, it was found that AY-18,672 (α,α-dimethylphenethylaminopropan-2-one) was more potent than AY-14,948 in causing a blockade of uptake of norepinephrine in the heart and these results are reported here. The methods used in the present study were identical to those described in the previous related publication[1].

The effects of compounds structurally related to AY-14,948 on the uptake and release of H^3-norepinephrine (H^3-NE) in the rat heart are shown in Table I. When the compounds were administered before the H^3-NE, AY-14,948 (20 mg/kg) caused a 49% decline in the H^3-NE. A decrease (33%) was observed in the H^3-NE after AY-18,672 at the lower dose of 2 mg/kg. AY-20,213 (20 mg/kg) and AY-20,214 (20 mg/kg) decreased the H^3-NE 32% and 22%, respectively. At 10 mg/kg AY-14,948, AY-18,672 and AY-20,213 caused declines of 30, 69 and 20%, respectively; no change was observed after AY-20,214. When AY-14,948, AY-20,213 and AY-20,214 at 20 mg/kg and AY-18,672 at 2 mg/kg were injected after the H^3-NE, no changes in the H^3-NE were observed after any of the compounds. Thus,

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